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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/316,199	05/21/1999	Michael J McCluskie	C1040/7006HC	7506

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/316,199	MCCLUSKIE ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-9,12,13,15-20,22,25-28,129,135-142 and 144-146* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-9, 12-13, 15-20, 22, 25-28, 129, 135-142 and 144-146* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 1/16/07 was entered.

Claims 1, 4-9, 12-13, 15-20, 22, 25-28, 129, 135-142 and 144-146 are pending in the present application, and they are examined on the merits herein.

Response to Amendment

The provisional rejection under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 145 of copending Application No. 10/888,886 is withdrawn because claim 145 is not included in the elected invention in the Amendment filed on 1/25/07.

Claim Rejections - 35 USC § 112

Amended claim 136 is still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing a mucosal immune response having the steps recited in claim 136, in which at least the oligonucleotide and the antigen are both administered intranasally, rectally, intravaginally, ocularly, or by inhalation to the subject;

does not reasonably provide enablement for a method for inducing a mucosal immune response in which the oligonucleotide and the antigen are not administered together to the same site as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for essentially

the same reasons already set forth in the Office action mailed on 7/28/05 (pages 4-8). ***This same rejection is restated below.***

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

When read in light of the specification, the sole purpose for a method of inducing a mucosal immune response in a subject as claimed is to attain prophylactic and/or therapeutic effects. There is no other disclosed use for the induction of a mucosal immune response in a subject. As enablement requires the specification to teach how to make and use the claimed invention, the instant specification is not enabled for the method as claimed for the following reasons.

1. The breadth of the claim

The claim is drawn to a method for inducing a mucosal immune response comprising administering to any mucosal surface of any subject in need of a mucosal immune response an effective amount for inducing a mucosal immune response of an oligonucleotide 8 to 100 nucleotides in length, having a sequence including at least the following formula: 5'-X1X2CGX3X4-3' wherein C is unmethylated, wherein X1, X2, X3, and X4 are nucleotides, any non-oligonucleotide mucosal adjuvant that is not an immune stimulating complex (ISCOM^{TM}), and any antigen, wherein the antigen is not

encoded in a nucleic acid vector and wherein the oligonucleotide and the non-oligonucleotide mucosal adjuvant are administered intranasally, rectally, intravaginally, ocularly, or by inhalation to the subject, and a cytokine is not administered to the subject. As written, the antigen and the oligonucleotide are not necessarily administered to the same site in the treated subject.

2. The state and the unpredictability of the prior art

At about the effective filing date of the present application (5/22/98), little was known whether a CpG motif containing oligonucleotide is capable of inducing a therapeutic mucosal immune response by itself in a subject against any antigen that the subject is exposed to, particularly the subject is exposed to the antigen at a mucosal surface that is different from that at which the CpG oligonucleotide is administered. Numerous post-filing publications after the effective filing date of the present application still only teach that CpG oligonucleotide is an effective mucosal adjuvant in mice when co-administered with protein antigens as evidenced by the teachings of Moldoveanu et al. (Vaccine 16:1216-1224, 1998; IDS), Davis et al. (J. Immunology 160:870-876, 1998; IDS), McCluskie et al. (J. Immunology 161:4463-4466, 1998; IDS); McCluskie et al. (Current Opinion in Invest. Drugs 2:35-39; 2001; IDS) and McCluskie et al. (Critical Reviews in Immunology 21:103-120, 2001; IDS). With respect to DNA vaccines containing a CpG motif, McCluskie et al. (Crit. Rev. Immunol. 19:303-329, 1999; Cited previously) have noted that the route of administration and DNA doses as well as numerous other factors such as the antigen, the dose of antigen, the co-expression of cytokines, and whether other adjuvant is used are also involved in determining the types

of host immune responses elicited (page 313, see the section titled "Role of CpG immunostimulatory sequences). Additionally, Caufield (WO 98/52962) also already demonstrated the lack of an adjuvant effect in a situation where a CpG containing oligonucleotide was injected in the opposite leg from where the antigen was injected (see example 5 on pages 25-26).

3. The amount of direction or guidance provided

The instant specification fails to provide sufficient guidance for a skilled artisan in the art on how to obtain any therapeutic mucosal immune response against any antigen in any subject, wherein the subject is exposed either passively or actively to the antigen at a different mucosal surface from which the CpG oligonucleotide is administered. There is no evidence in the prior art at the effective filing date of the present application or in the instant disclosure demonstrate that a CpG motif containing oligonucleotide by itself is capable of inducing an effective antigen-specific mucosal immune response that yields prophylactic and/or therapeutic effects in a subject against any antigen that the subject is exposed to. Nor is there any evidence of record indicating or suggesting that a CpG oligonucleotide has an effective adjuvant effect for any antigen that is not co-administered or administered at the same site (including a mucosal surface) as that of the CpG oligonucleotide. As already noted above, Caufield (WO 98/52962) already demonstrated the lack of an adjuvant effect in a situation where a CpG containing oligonucleotide was injected in the opposite leg from where the antigen was injected (see example 5 on pages 25-26). In addition, the instant specification teaches explicitly that CpG alone did not induce IgA in lung washes, however it induced IgA in the feces

but only in some animals (see page 63, lines 20-29), and there is no evidence that the detectable IgA is effective to yield any prophylactic and/or therapeutic effects that are contemplated by Applicants. Even several years after the effective filing date of the present application, McCluskie et al. (Current Opinion in Invest. Drugs 2:35-39; 2001; IDS) still state "[w]e and others have recently shown CpG DNA to be an effective mucosal adjuvant in mice when co-administered with protein antigens" (page 35, col. 2, bottom of second paragraph). It is further noted that the physiological art is recognized as unpredictable (MPEP 2164.03).

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability of the relevant art for the attainment of a therapeutic mucosal immune response against any antigen in any subject, wherein the subject is exposed either passively or actively to the antigen at a different mucosal surface from which the CpG oligonucleotide is administered, and the breadth of the claim, it would have required undue experimentation for one skilled in the art to **make and use** the method as broadly claimed.

Response to Arguments

Applicants' argument with respect the above rejection in the Amendment filed on 1/16/07 (page 9) has been fully considered but it is respectfully not found persuasive.

Applicants argue basically amended claim 136 recites that the oligonucleotide and the antigen are both administered intranasally, rectally, intravaginally, ocularly, or by inhalation to the subject.

It is noted that amended claim 136 recites "and wherein the oligonucleotide and the non-oligonucleotide mucosal adjuvant are both administered". As written, the claim is not limited that the antigen is administered together with the oligonucleotide and the non-oligonucleotide mucosal adjuvant to the same site by the recited routes of delivery.

Accordingly, amended claim 136 is still rejected under 35 U.S.C. 112, first paragraph, for the reasons already set forth above.

Claim Rejections - 35 USC § 103

Claims 1, 4-9, 12-13, 15-20, 22, 26-28, 129, 135-142 and 144-146 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al. (US 6,239,116; Cited previously) in view of Hutcherson et al. (US 6,727,230 B1; Cited previously) **or** Agrawal et al. (US 6,426,334; Cited previously) and evidenced by McCluskie et al. (Vaccine 19:413-422, 2001; Cited previously) for the same reasons already set forth in the Office Action mailed on 7/12/06 (pages 9-13). ***The same rejection is restated below.***

Krieg et al discloses a method of stimulating immune activation by administering an isolated immunostimulatory nucleic acid sequence containing a CpG motif represented by the formula: 5'-N1X1CpGX2N2-3', wherein at least one nucleotide separates consecutive CpGs; X1 is adenine, guanine, or thymine; X2 is cytosine or thymine; N is any nucleotide and N1+N2 is from about 0-26 bases with the proviso that N1 and N2 do not contain a CCGG quadmer or more than one CCG or CGG trimer; and the nucleic acid sequence is from about 8-30 bases in length and wherein the immune activation effects predominantly a Th1 pattern of immune activation (see Summary of

the Invention). Krieg et al further teaches that the nucleic acid sequence can be administered to stimulate a subject's response to a vaccine to ameliorate disorders such as cancer, viral, fungal, bacterial or parasitic infection, specifically the nucleic acid sequence can be administered to a subject in conjunction with a particular allergen as a type of desensitization therapy to treat the occurrence of an allergic reaction associated with an asthmatic disorder (col. 6, line 63 continues to line 7 of col. 7). Infectious virus, bacteria, fungi are listed in columns 10-11. The CpG oligonucleotides are stabilized by incorporating a phosphate backbone modification, for example a phosphorothioate or phosphorodithioate modification at the 5' end or 3' end (col. 14, lines 3-32). Krieg et al also specifically teaches the sequence 1826 having the sequence TCCATGACGTTCCTGACGTT is a strong immune activating sequence and is a superb adjuvant, with efficacy comparable or superior to complete Freund's, but without apparent toxicity (col. 22, lines 54-62). Krieg et al. further teaches that the immunostimulatory nucleic acid sequence can be administered to a subject slightly before or at the same time as the vaccine, and that a conventional adjuvant (e.g., aluminum precipitates) may optionally be administered in conjunction with the vaccine, which is minimally comprised of an antigen, as the conventional adjuvant may further improve the vaccination by enhancing antigen absorption (col. 45, lines 37-46). Routes of administering the immunostimulatory nucleic acid include oral and transdermal and others (col. 46, lines 55-64). It is also noted that a subject having an immune system deficiency such as a subject having a cancer or an infection is a subject in need of at least a mucosal immune response. Krieg et al further discloses that for administration

in vivo, nucleic acids may be associated with a target cell specific binding agent or be encapsulated in liposomes or virosomes using well known techniques (col. 13, lines 42-47; col. 45, lines 6-17).

Krieg et al. does not disclose specifically the recited routes of administration, even though Krieg et al. teaches that any administration route to a subject can be used, with the preferred routes of administration include oral and transdermal. Krieg et al. also does not teach specifically further administering a boost of the oligonucleotide or a boost of the oligonucleotide and a non-oligonucleotide mucosal adjuvant.

However, at the effective filing date of the present application Hutcheson et al already taught delivering to an infectious subject or a tumor bearing subject an effective amount of a synthetic or ISIS oligonucleotide containing an unmethylated CpG motif by various administration routes including opthalmically, intranasally, rectally, vaginally, orally as well as inhalation to stimulate a cell mediated immune response (see at least Summary of the Invention; col. 7, lines 48-66; Table 1 and Sequence listing). Hutcheson et al. further teaches that dosing is dependent on severity and responsiveness of the condition to be treated, and will normally be one or more doses per day, with course of treatment lasting from several days to several months, and that an ordinary skilled artisan can easily determine the optimum dosages, dosing methodologies and repetition rates (col. 8, lines 27-34).

Agrawal et al. also taught delivering to an infectious subject or a tumor bearing subject an effective amount of a synthetic oligonucleotide containing an unmethylated CpG motif through various modes of administration that include oral, topical, intranasal,

intrarectal among others to stimulate an immune response (col.5, lines 39-43). Agrawal et al. further teaches that administration of the oligonucleotides can be carried out using known procedures at dosages and for periods of time effective to reduce symptoms (col. 5, lines 46-48).

Accordingly, it would have been obvious for an ordinary skilled artisan, particularly an investigator in the art of vaccine, to modify a method of stimulating immune activation of Krieg et al. by also delivering their vaccine composition containing an isolated immunostimulatory nucleic acid sequence at least intranasally, rectally, vaginally, orally as well as inhalation in light of the teachings of either Hutcherson et al. or Agrawal et al. Additionally, it would also have been obvious for an ordinary skilled artisan to administer the composition one or more doses or repetition rates to attain the desired effects in light of the teachings of either Hutcherson et al. or Agrawal et al.

An ordinary skilled artisan would have been motivated to carry out the above modifications because these specific routes of delivery have been routinely and successfully used for delivering for a synthetic oligonucleotide containing an unmethylated CpG motif to induce an immune response in an infectious subject or a tumor bearing subject as taught by either Hutcherson et al. or Agrawal et al. Furthermore, both Hutcherson et al. and Agrawal et al. teach clearly that procedures at dosages and for periods of time effective to attain the desired effects are well known in the art.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Krieg et al., Hutcherson et al. or Agrawal et al., coupled with a

high level of skill for an ordinary skilled artisan in the relevant art. Particularly, since the modified method that is based on the combined teachings Krieg et al., and either Hutcherson et al. or Agrawal et al. has the same method steps and starting materials as those of the present application, an induction of a mucosal immune response would be expected to occur. Moreover, this is supported by the factual evidence established by McCluskie et al which shows that oligonucleotides containing CpG motifs can induce an antigen-specific mucosal immune response in a subject upon oral, intrarectal or intranasal delivery of an antigen together with the CpG oligonucleotides (see at least Figure 2).

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments with respect the above rejection in the Amendment filed on 1/16/07 (pages 10-12) have been fully considered but they are respectfully not found persuasive.

1. Applicants that that Hutcherson does not teach the delivery of an unmethylated CpG oligonuclotide, and therefore an ordinary skilled artisan would not combine the references as the Examiner has suggested, and only based on hindsight.. Applicants further argue that the Hutcherson patent does not teach subjects in need of mucosal immune responses, and that the combination of references does not teach administration to subjects in need of a mucosal immune response. Applicants also

argue that the Examiner has not provide any evidence to support his statement that a subject having an immune system deficiency such as a subject having a cancer or an infection is a subject in need of at least a mucosal immune response.

Please note that the synthetic or ISIS oligonucleotides taught by Hutcherson et al must contain an unmethylated CpG motif (see at least Table 1 and Sequence listing), because if the C is methylated, the nucleotide would no longer be called or labeled as C. Additionally, there is no teachings in the Hutcherson et al patent indicating or suggesting that the CpG motif in the synthetic or ISIS oligonucleotides is methylated. Furthermore, please also note that the above rejection is under 35 U.S.C. 103(a), and therefore none of the cited references has to teach every elements of the claims.

As for applicants argument regarding that the cited references do not provide any suggestion or motivation to make the combination argued by the examiner, Examiner would like to recite a paragraph from *in re Oetiker,* 977, F.2d 1443, 1448 (Fed. Cir. 1992).

> "[T]here must be some teaching, reason, suggestion, or motivation found "in the prior art" or "in the prior art references" to make a combination to render an invention obvious within the meaning of 35 U.S.C. 103 (1998). Similar language appear in a number of opinions and if taken literally would mean that an invention cannot be held to have been obvious unless something specific in a prior art reference would lead an inventor to combine the teachings therein with another piece of prior art. This restrictive understanding of the concept of obviousness is clearly wrong.... While there must be some teaching, reason, suggestion, or motivation to combine existing elements to produce the claimed device, it is not necessary that the cited references or prior art specifically suggest making the combination.... In sum, it is off the mark for litigants to argue, as many do, that an invention cannot be held to have been obvious unless a suggestion to
> combine the prior art teachings is found in a specific reference."

Although the cited artisans do not specifically point out a motivation to in their disclosure, an ordinarily skilled artisan would have been able to identify the need for the combination of the teachings without the disclosure of the instant application. Heller et al. disclose an electronically addressable array where, "...variety of molecular biological reactions including linear and exponential multiplication or amplification of target DNA and RNA molecules can be carried out" (lines 16-19). The reference further states that many types of DNA modifying enzymes can be used, such as but not limited to restriction endonucleases, DNA or RNA polymerases, and ligases at any desired micro-locations on device.

It must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For this instance, an ordinary skilled artisan would have been motivated to carry out the modifications set forth above because these specific routes of delivery have been routinely and successfully used for delivering for a synthetic oligonucleotide containing an unmethylated CpG motif to induce an immune response in an infectious subject or a tumor bearing subject as taught by either Hutcherson et al. or Agrawal et al. Furthermore, both Hutcherson et al. and Agrawal et al. teach clearly that procedures at dosages and for periods of time effective to attain the desired effects are well known in the art.

With respect to the issue that that a subject having an immune system deficiency such as a subject having a cancer or an infection is a subject in need of at least a mucosal immune response, because noted that when read in light of the specification a subject in need of at least a mucosal immune response is a subject at risk of developing an allergic reaction, an infectious disease or cancer or a subject has an infectious disease, a cancer, an allergy or is an asthmatic (see at least page 7, lines 19-23). Krieg et al clearly defines the phrase "an immune system deficiency" to be a disease or disorder in which the subjet"s immune system is not functioning in normal capacity or in which it would be useful to boost a subject's immune response for example to eliminate a tumor or cancer or an infection in a subject (see at least col. 10, lines 23-31).

With respect to amended claim 138, please also note that Krieg et al. teaches specifically that the immunostimulatory nucleic acid sequence can be used to treat, prevent or ameliorate other disorders (e.g., a tumor or cancer or a viral, fungal, bacterial or parasitic infection), see at least col. 6, lines 63-66. A subject that is passively exposed to an antigen includes a subject having an infectious disease, a cancer, an allergy or is an asthmatic (see instant specification, page 7, lines 19-23).

2. Applicants argue that Agrawal does not describe the combination of an oligonucelotide with an antigen to produce an antigen specific immune response, and an ordinary skilled artisan would not have substituted the teachings of Krieg et al into the teachings of Agrawal of inducing an IL-12 immune response. Applicants further argue that the Agrawal patent does not teach subjects in need of mucosal immune

responses, and that the combination of references does not teach administration to subjects in need of a mucosal immune response. Applicants also argue that the Examiner has not provide any evidence to support his statement that a subject having an immune system deficiency such as a subject having a cancer or an infection is a subject in need of at least a mucosal immune response.

Once again, please note that the above rejection is under 35 U.S.C. 103(a), and therefore none of the cited references has to teach every elements of the claims. Krieg et al. does not disclose specifically the recited routes of administration, even though Krieg et al. teaches that any administration route to a subject can be used, with the preferred routes of administration include oral and transdermal. However, Agrawal et al. already taught delivering to an infectious subject or a tumor bearing subject an effective amount of a synthetic oligonucleotide containing an unmethylated CpG motif through various modes of administration that include oral, topical, intranasal, intrarectal among others to stimulate an immune response (col.5, lines 39-43). Agrawal et al. further teaches that administration of the oligonucleotides can be carried out using known procedures at dosages and for periods of time effective to reduce symptoms (col. 5, lines 46-48). As already noted above, an ordinary skilled artisan would have been motivated to carry out the modifications set forth above because these specific routes of delivery have been routinely and successfully used for delivering for a synthetic oligonucleotide containing an unmethylated CpG motif to induce an immune response in an infectious subject or a tumor bearing subject as taught by either Hutcherson et al. or Agrawal et al. Furthermore, both Hutcherson et al. and Agrawal et

al. teach clearly that procedures at dosages and for periods of time effective to attain the desired effects are well known in the art.

Accordingly, claims 1, 4-9, 12-13, 15-20, 22, 26-28, 129, 135-142 and 144-146 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al. (US 6,239,116; Cited previously) in view of Hutcherson et al. (US 6,727,230 B1; Cited previously) **or** Agrawal et al. (US 6,426,334; Cited previously) and evidenced by McCluskie et al. (Vaccine 19:413-422, 2001; Cited previously) for the same reasons already set forth in the Office Action mailed on 7/12/06 (pages 9-13).

Claim 25 is still rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al. (US 6,239,116; Cited previously) in view of Hutcherson et al. (US 6,727,230 B1; Cited previously) **or** Agrawal et al. (US 6,426,334; Cited previously) and evidenced by McCluskie et al. (Vaccine 19:413-422, 2001; Cited previously) as applied to claims 1, 4-9, 12-13, 15-20, 22, 26-28, 129, 135-142 and 144-146 above, and further in view of Craig (US 6,689,757; Cited previously) for the same reasons already set forth in the Office Action mailed on 7/12/06 (pages 13-15). ***The same rejection is restated below.***

The combined teachings of Krieg et al. with either Hutcherson et al. or Agrawal et al. were presented above. However, none of the references teaches specifically a method further comprising administering a B-7 costimulatory molecule.

At the effective filing date of the present application, Craig already taught methods for vaccinating a mammal against a disease using additional factors that

include cytokines and/**or** co-stimulatory molecules such as B7-1, B7-2, ICAM-1 and ICAM-3 in conjunction with a nucleic acid and antigen (col. 6, lines 35-49).

Accordingly, it would have been obvious for an ordinary skilled artisan to further modify the method resulting from the combined teachings of Krieg et al. and either Hutcherson et al. or Agrawal et al. by further employing a co-stimulatory molecule such as B7-1, B7-2 in light of the teachings of Craig.

An ordinary skilled artisan would have been motivated to carry out the above modification because the further administration of co-stimulatory molecules such as B7-1 and B7-2 would further enhance the induced immune response in the subject as taught by Craig.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Krieg et al. with either Hucherson et al. or Agrawal et al., along with Craig, and coupled with a high level of skill possessed by an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments with respect the above rejection in the Amendment filed on 1/16/07 (page 12) have been fully considered but they are respectfully not found persuasive.

Applicants argue basically that Craig et al does not cure the deficiencies in the combination of references set forth above, and that Craig et al. requires dual delivery of an epitope or antigen in its peptide or polypeptide form and a nucleic acid encoded epitope.

With respect to the deficiencies of the combination of references, please refer to the Examiner's rebuttal to the same Applicant's arguments above. As already noted in the above rejection, an ordinary skilled artisan would have been motivated to further modify the method resulting from the combined teachings of Krieg et al. and either Hutcherson et al. or Agrawal et al. by further employing a co-stimulatory molecule such as B7-1, B7-2 because the further administration of co-stimulatory molecules such as B7-1 and B7-2 would further enhance the induced immune response in the subject as taught by Craig.

Accordingly, claim 25 is still rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al. (US 6,239,116; Cited previously) in view of Hutcherson et al. (US 6,727,230 B1; Cited previously) **or** Agrawal et al. (US 6,426,334; Cited previously) and evidenced by McCluskie et al. (Vaccine 19:413-422, 2001; Cited previously) as applied to claims 1, 4-9, 12-13, 15-20, 22, 26-28, 129, 135-142 and 144-146 above, and further in view of Craig (US 6,689,757; Cited previously) for the same reasons already set forth in the Office Action mailed on 7/12/06 (pages 13-15).

Claims 136 and 142 are still rejected under 35 U.S.C. 103(a) as being unpatentable over Briles et al. (U.S. Patent No. 6,042,838) in view of Krieg et al. (U.S.

Patent No. 6,194,388; IDS) and evidenced by McCluskie et al. (Vaccine 19:413-422, 2001; Cited previously) for the same reasons already set forth in the Office Aciton mailed on 7/12/06 (pages 15-18). ***The same rejection is restated below.***

Briles et al. discloses an immunogenic composition and a method for eliciting an immunological response against pneumococcal surface protein A (PSPA) in a host susceptible to *Streptococcus pneumoniae* by intranasally administering to the host an effective amount of PSPA in the form of a killed whole pneumococci, a lysate of pneumococci or an isolated PSPA or an immunogenic fragment thereof in the presence of an adjuvant, with cholera toxin B as a preferred adjuvant, to protect a host against pneumoccocal colonization and/or systemic infection (see summary of invention, col. 1-7). Briles et al. also teaches that immunostimulatory agents or adjuvants have been used to improve the host immune responses to vaccines, these include intrinsic adjuvants such as lipopolysaccharides which normally are the components of the killed or attenuated bacteria used as vaccines or extrinsic adjuvants such as aluminum hydroxide, LPS, Freund's complete adjuvant and others which are immunomodulators which are typically non-covalently linked to antigens and are formulated to enhance the host immune responses. Briles et al. further discloses that the immunogenic composition can be prepared as inhalables, sprays and that pump spray or nasal spray or squeeze dispensers (a device) for dispensing a metered dose or a dose with a particular particle or droplet size are commercial available for mucosal administration (col. 3, lines 32-52). Briles et al. further teaches that useful surfactants for the immunogenic composition include polyoxyethylene derivatives of fatty acid partial esters

of sorbitol anhydrides such as Tween 80, Polyoxyl 40 Stearate and others to enhance absorption (col. 6, lines 14-21). Briles et al. further teaches that specific IgA antibodies are induced in secretions of the intestinal, respiratory, and genital tracts, as well as predominantly IgA antibody secreting cells in the intestinal lamina propria and salivary glands. Strong circulatory immune responses are also induced with IgG and IgA antibodies in the serum, and IgG and IgA antibody-secreting cells in the spleen (col. 8, lines 14-34, and examples).

Briles et al. does not teach the use of any oligonucleotide 8 to 100 nucleotides in length, having a sequence including at least the formula: 5'-X1X2CGX3X4-3', wherein C is unmethylated, as an adjuvant in a composition or a method for inducing mucosal immunity to an antigen in a mammalian host via intranasal administration.

However, at the effective filing date of the present application, Krieg et al. discloses various immunostimulatory oligonucleotides having the CpG motifs, among which is an oligonucleotide comprising the sequence AACGTT (see Table 1). For facilitating uptake into cells, the immunostimulatory oligonucleotides are preferably in the range of 8 to 40 base pairs in size (col. 6, lines 18-20). Additionally, Krieg et al. teaches that the immunostimulatory oligonucleotides can be used in conjunction with a vaccine or an antigen in a pharmaceutically acceptable carrier, as an adjuvant to boost a mammal's immune response to effect better response from the vaccine (col. 17, line 65 continues to line 3 of col. 18; and the claims).

Accordingly, it would have been obvious for an ordinary skilled artisan, particularly an investigator in the art of vaccine, to modify the immunogenic composition

and the method for inducing mucosal immunity against pneumococcal colonization and systemic infection taught by Briles et al. by utilizing at least an immunostimulatory oligonucleotide having the sequence AACGTT taught by Krieg et al. as an adjuvant.

An ordinary skilled artisan would have been motivated to carry out the above modification because Krieg et al. teaches clearly that an immunomodulatory oligonucleotide having a CpG motif can be used in conjunction with a vaccine or an antigen in a pharmaceutically acceptable carrier, as an adjuvant to boost a mammal's immune response to effect better response from the vaccine (col. 17, line 65 continues to line 3 of col. 18; and the claims).

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Briles et al., Krieg et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art. Particularly, since the modified method that is based on the combined teachings Briles et al. and Krieg et al., has the same method steps and starting materials as those of the present application, an induction of a mucosal immune response would be expected to occur. Moreover, this is supported by the factual evidence established by McCluskie et al which shows that oligonucleotides containing CpG motifs can induce an antigen-specific mucosal immune response in a subject upon oral, intrarectal or intranasal delivery of an antigen together with the CpG oligonucleotides (see at least Figure 2).

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments with respect the above rejection in the Amendment filed on 1/16/07 (pages 12-13) have been fully considered but they are respectfully not found persuasive.

1. With respect to claim 136, Applicants argue that Briles et al. teaches mucosal administration to the respiratory mucosa, gingival mucosa, alveolar mucosa, perlingual mucosa, sublingual mucosa, or via the mouth or respiratory tract, with intranasal administration being preferred. Krieg et al teaches administration by injection, transdermal or oral route. Therefore, the combination of the references does not teach administration of oligonucleotide and non-oligonucleotide mucosal adjuvant via the same route, because the only common administration route between the references is oral administration and this is excluded in claim 136.

It appears that Applicants argue the teachings of Briles et al. and Krieg et al. completely separately one from the other. As already noted above, an ordinary skilled artisan, particularly an investigator in the art of vaccine, to modify the immunogenic composition and the method for inducing mucosal immunity against pneumococcal colonization and systemic infection taught by Briles et al. by utilizing at least an immunostimulatory oligonucleotide having the sequence AACGTT taught by Krieg et al. as an adjuvant because Krieg et al. teaches clearly that an immunomodulatory oligonucleotide having a CpG motif can be used in conjunction with a vaccine or an antigen in a pharmaceutically acceptable carrier, as an adjuvant to boost a mammal's immune response to effect better response from the vaccine. Additionally, please note

that Briles et al. also teaches that immunostimulatory agents or adjuvants have been used to improve the host immune responses to vaccines, these include intrinsic adjuvants such as lipopolysaccharides which normally are the components of the killed or attenuated bacteria used as vaccines or extrinsic adjuvants such as aluminum hydroxide, LPS, Freund's complete adjuvant and others which are immunomodulators which are typically non-covalently linked to antigens and are formulated to enhance the host immune responses. In the overall context of the teachings of Briles et al. there is no rational or suggestion that why immunostimulatory agents or adjuvants including the use of immunomodulatory oligonucleotides and at least the preferred adjuvant cholera toxin B be administered by different routes of delivery.

2. With respect to claim 137, Applicants argue that the combination of the references does not teach administration of viral antigen to subjects in need of a mucosal immune response. Briles et al teaches administration of bacterial PspA or immunogenic fragments thereof, while Krieg et al. teaches administration of antigens generally.

Applicant's argument is moot because the above rejection does not contain claim 137.

3. With respect to claim 138, the combination of references does not teach passively exposing the subject to antigen. Briles et al teaches active immunization with

PspA or fragments thereof, while Krieg et al also teach active administration of antigens generally in the context of a vaccine.

Applicant's argument is moot because the above rejection does not contain claim 138.

Conclusions

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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QUANG NGUYEN, PH.D.
PRIMARY EXAMINER